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Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence

Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) type represent ~7% of all non-Hodgkin's lymphomas in the western world and can arise at any extranodal site. At least one-third of them present as a primary gastric lymphoma, which in approximately two-thirds of cases is associated with a chronic *Helicobacter pylori* infection [1].

diagnosis

The most common presenting symptoms of a gastric MALT lymphoma are non-specific upper gastrointestinal complaints that often lead to an endoscopy usually revealing non-specific gastritis or peptic ulcer with mass lesions being unusual [2, 3].

Diagnosis is based on the histopathological evaluation of the gastric biopsies [III, A]. The diagnosis should be in accordance with the current World Health Organisation (WHO) classification and accurate assessment of a potential associated large B-cell lymphoma is essential [4]. The diagnosis should, therefore, be confirmed by an expert haematopathologist [5]. It should be noted that the term 'high grade MALT lymphomas' is no longer accepted in the current WHO classification, hence cases with solid or sheet-like proliferation of transformed large cells have to be diagnosed as diffuse large B-cell lymphoma [4]. Differentiation from other indolent lymphomas is not always straightforward and a minimum immunohistochemistry panel should include CD20, CD10, CD5 and cyclin D1 [IV, B]. It is noteworthy that lymphoepithelial lesions, despite being very typical of MALT lymphoma, are neither essential for the diagnosis nor pathognomonic, as they can be seen under some reactive conditions as well as in other lymphoma subtypes.

If the presence of active *H. pylori* infection is not demonstrated by histochemistry, it must be ruled out by serology, urea breath test and/or stool antigen test [5, 6].

In addition to routine histology and immunohistochemistry, fluorescence *in situ* hybridisation studies for detection of *t*(11;18) (p21;p21) may be useful for identifying patients who are unlikely to respond to antibiotic therapy [III, B] [5, 6].

staging and risk assessment

The question of which is the best system for the staging of gastric MALT lymphoma is controversial [2, 6]. The 'Lugano staging system' has been widely used in the past two decades, but more modern systems have been proposed, such as the 'Paris staging system', which describes more accurately the depth of gastric wall involvement, a parameter that may predict the lymphoma response to *H. pylori* eradication (Table 1) [7, 8].

The initial staging procedures must include an esophagogastroduodenoscopy with multiple biopsies taken from each region of the stomach, duodenum and gastroesophageal junction and from any site with an abnormal appearance. Endoscopic ultrasound is recommended to evaluate the regional lymph nodes and gastric wall infiltration [III, A] [2, 3, 5, 6, 9]. Work-up studies should include history and physical examination, including lymph node regions, eye and ear, nose and throat areas, liver and spleen evaluation; complete blood counts, basic biochemical studies, which may include evaluation of renal and liver function, lactate dehydrogenase and β2-microglobulin, serum protein immunofixation, human immunodeficiency virus, hepatitis C virus and hepatitis B virus serology, computed tomography scan of the chest, abdomen and pelvis [IV, B] [2, 3, 5, 6, 9]. A bone marrow aspirate and biopsy is recommended [IV, B] [5]. The value of a positron

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Table 1. Comparison of the Lugano and Paris staging systems for gastrointestinal tract lymphoma

Lugano staging system [7]	Paris staging system [8]	Tumour extension
Stage I = confined to the GI tract (single primary or multiple, non-contiguous)	T1m N0 M0	*Mucosa*
	T1sm N0 M0	*Submucosa*
	T2 N0 M0	*Muscularis propria*
	T3 N0 M0	*Serosa*
Stage II = extending into abdomen	T1-3 N1 M0	*Perigastric lymph nodes*
II_1 = local nodal involvement	T1-3 N2 M0	*More distant regional nodes*
II_2 = distant nodal involvement		
Stage II_E = penetration of serosa to involve adjacent organs or tissues	T4 N0-2 M0	*Invasion of adjacent structures with or without abdominal lymph nodes*
Stage IV = disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement	T1-4 N3 M0	*Extra-abdominal lymph nodes*
	T1-4 N0-3 M1	*And/or additional distant (non-continuous) gastrointestinal sites*
	T1-4 N0-3 M2	*Or non-gastrointestinal sites*
	T1-4 N0-3 M0-2 BX	*Bone marrow not assessed*
	T1-4 N0-3 M0-2 B0	*Bone marrow not involved*
	T1-4 N0-3 M2 B1	*Bone marrow involvement*

GI, gastrointestinal; T describes the gastric wall infiltration; N describes the regional lymph node involvement; M describes distant dissemination; B describes the bone marrow assessment. Reproduced from: Rohatiner A et al. [7] With permission of Oxford University Press. Ruskone-Fourmestrauxet al. [8]. With permission from BMJ Publishing Group Ltd.

emission tomography scan is controversial and has little clinical utility [IV, D] [5].

treatment plan

Helicobacter pylori eradication therapy must be given to all gastric MALT lymphomas, independently of stage [5]. Anti-*helicobacter* regimens combining proton-pump inhibitor (PPI) plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days are usually highly effective [10]. The outcome of the eradication therapy should be checked by a urea breath test (or by a monoclonal stool antigen test) at least 6 weeks after eradication therapy and at least 2 weeks after PPI withdrawal. In case of unsuccessful *H. pylori* eradication, a second-line therapy should be attempted with alternative triple- or quadruple-therapy regimens of PPI plus antibiotics [1, 6].

Eradication of *H. pylori* with antibiotics should be the sole initial therapy for a localised *H. pylori*-positive gastric MALT lymphoma, where this treatment can induce lymphoma regression and long-term clinical disease control in most patients [II, A]. The length of time necessary to obtain a remission can span from very few months to >12 months. It is reasonable to wait for at least 12 months before starting another treatment in patients who achieve a clinical and endoscopic remission together with eradication of *H. pylori*, albeit having persistent (residual) lymphoma at the histological level [III, B] [6]. Several studies of post-antibiotic molecular follow-up have shown the frequent persistence of monoclonal B-cells after histological regression of the lymphoma [1, 6].

In *H. pylori*-negative cases, a regression of the lymphoma after antibiotic treatment is unlikely and the immediate start of oncological treatments (see below) should be considered, but the administration of an anti-*helicobacter* regimen may be worthwhile since occasional lymphoma responses have been reported (possibly due to a false-negative test or to infection by other *Helicobacter* species) [6]. In these *H. pylori*-negative patients, an oncological treatment (usually radiotherapy as described below) should, however, be considered if no signs of lymphoma regression are seen at a repeat endoscopy assessment 2 to 3 months after antibiotics administration [6].

In patients who do not achieve a lymphoma regression following antibiotic therapy, irradiation and systemic oncological therapies should be applied depending on the stage of disease. Radiotherapy might be the preferred option for localised stage. Excellent disease control using radiation therapy alone has been reported by several institutions supporting the use of moderate-dose involved-field radiotherapy (24–30 Gy radiation to the stomach and perigastric nodes given in 3 to 4 weeks) [III, B] [11, 12].

Chemotherapy and/or immunotherapy are effective in patients with MALT lymphoma of all stages. Chemoimmunotherapy should be preferred in case of histological transformation, contraindications to radiotherapy, and vice versa. However, there is no definitive evidence to guide the choice between radiotherapy and systemic treatment in localised gastric MALT lymphoma, which depends very much on the local expertise of the attending physicians [1, 5]. Patients with $t(11;18)$ will most probably be unresponsive to alkylating agents as a sole treatment [1, 6]. Surgery has not been shown to achieve superior results in comparison with more conservative approaches in various trials. It may impair the quality of life and no longer has a role in the initial treatment [13].

Patients with symptomatic systemic disease should be considered for systemic treatment [III, A]. As in other disseminated low-grade lymphomas, rituximab plus chemotherapy would then be the most appropriate choice when treatment is needed.

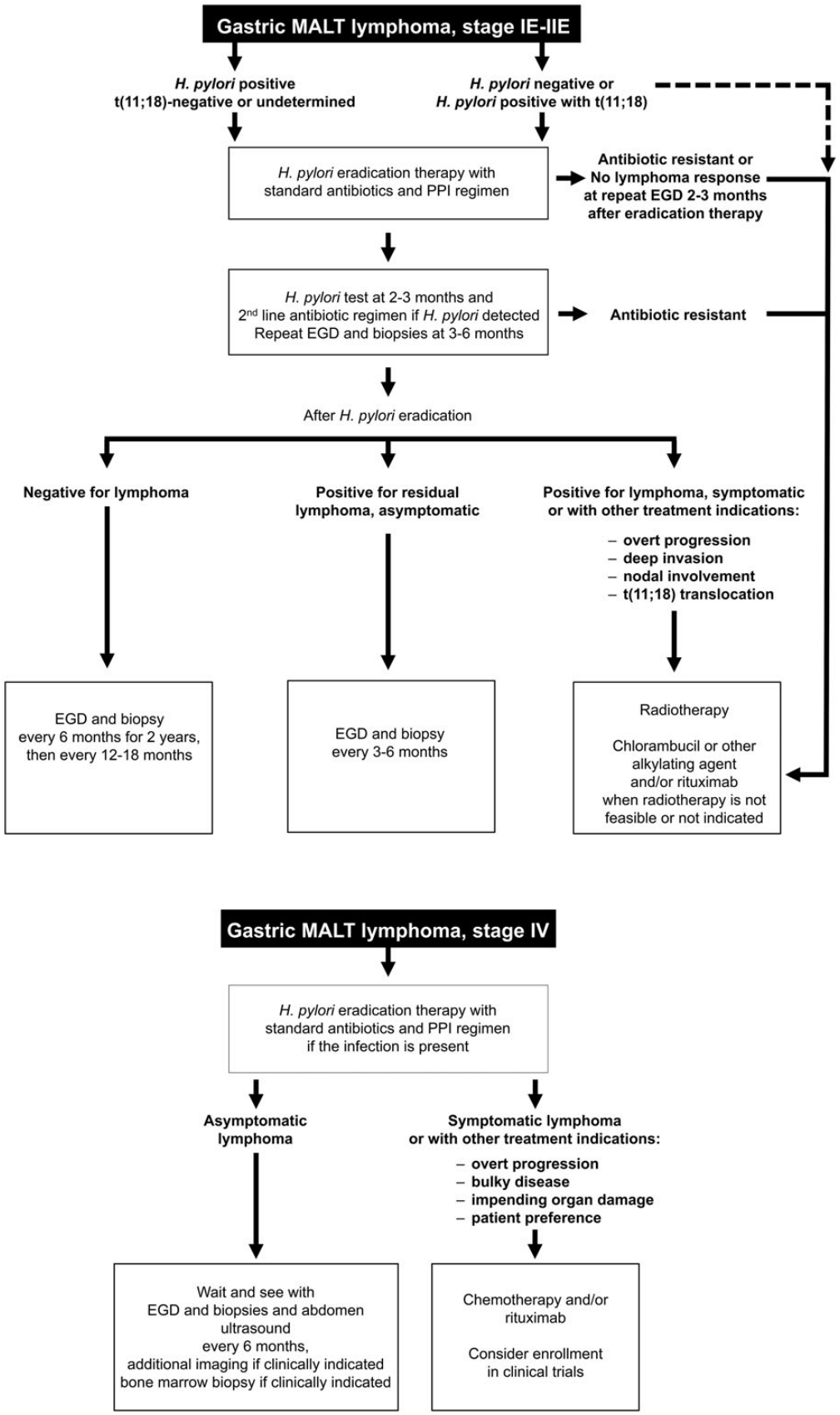

Figure 1. Treatment algorithms for either localised or advanced gastric MALT lymphoma (stage is defined according to the Lugano system described in Table 1).

Only a few compounds and regimens have been tested specifically in MALT lymphomas. Oral alkylating agents (either cyclophosphamide or chlorambucil) or purine nucleoside analogues (fludarabine, cladribine) and the combination of rituximab and bendamustine have shown a high rate of disease control in non-randomised studies. The activity of rituximab has also been demonstrated in phase II studies [14] and its efficacy in combination with chlorambucil has been proven in a randomised study [II, A] [15]. This combination was very well-tolerated but no overall survival benefit has been shown [15] and there is not yet an accepted standard chemotherapy to be recommended. It should, however, be mentioned that treatment with purine analogues might be associated with an increased risk of secondary myelodysplasia. There are no data supporting a rituximab maintenance strategy. Aggressive anthracycline-containing regimens are not usually necessary and should be reserved for the few patients with a very aggressive clinical course or histological transformation [3]. Treatment algorithms summarising the above discussed management strategies for either localised or advanced gastric MALT lymphoma are shown in Figure 1.

personalised medicine

Absence of *H. pylori*, deep invasion of the gastric wall (beyond the sub-mucosa), regional lymph node involvement, the presence of chromosomal translocations that result in deregulation of MALT1 or Bcl-10 and other genetic features (such as overexpression of miR-142-5p and miR-155) can be associated with a reduced probability of lymphoma regression after antibiotics [1–3, 16–18]. As discussed above, detection of *t* (11;18) may also help to distinguish patients who may not respond to alkylating agents alone. Nevertheless, in this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

response evaluation and follow-up

Histological evaluation of repeat biopsies remains an essential follow-up procedure to exclude either the possibility of persistent significant disease or, particularly in patients with persistent *H. pylori* infection, the appearance of early epithelial changes, which may be related to gastric carcinoma. Unfortunately, the interpretation of lymphoid infiltrate in post-treatment gastric biopsies can be very difficult and there are no uniform criteria for the definition of histological remission. Comparison with previous biopsies should be carried out to assess response, and we recommend the GELA (Group d'Etude des Lymphomes de l'Adult) scoring system (Table 2) as a reproducible method [IV, B] [19].

Following the documentation of the achieved *H. pylori* eradication, a strict endoscopic follow-up is recommended, with multiple biopsies taken 2 to 3 months after treatment to rule out tumour progression, and subsequently (twice per year for 2 years) to monitor the histological regression of the lymphoma.

Gastric MALT lymphomas have a limited tendency to distant spreading and to histological transformation. Transient, apparent histological relapses are occasionally observed in endoscopic follow-up biopsies, but they have to be sustained and progressive in order to be considered a relapse, as they tend to be self-limiting, especially in the absence of *H. pylori* reinfection. Hence, in the case of persistent but stable residual disease or histological relapse (without distant dissemination and/or gross endoscopic tumour), a watch-and-wait policy appears to be safe [IV, C] [16, 20–22]. Nevertheless, a long-term careful endoscopic and systemic follow-up (clinical examination, blood counts and minimal adequate radiological or ultrasound examinations every 12–18 months) is recommended for all patients. Indeed, the risk of gastric adenocarcinoma among patients diagnosed with gastric MALT lymphomas has been reported to be sixfold higher than in the general population [23] and also the risk of other non-Hodgkin's lymphomas may be increased [24].

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Dr Zucca has reported research support from Roche, Mundipharma, Janssen, Novartis, GSK and Celgene.
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Table 2. GELA grading system proposed to define the histological response of gastric MALT lymphoma after *H. pylori* eradication [17]

Response (score)	Description	Histological Characteristics
CR	Complete histological remission	*Normal or empty LP and/or fibrosis with absent or scattered plasma cells and small lymphoid cells in the LP, no LEL*
pMRD	Probable minimal residual disease	*Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM, no LEL*
rRD	Responding residual disease	*Focal empty LP and/or fibrosis with dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP, focal LEL or absent*
NC	No change	*Dense, diffuse or nodular lymphoid infiltrate, LEL usually present*

LEL, lymphoepithelial lesions; LP, lamina propria; MM, muscularis mucosa; SM, submucosa.
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Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

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